Remarks

Claims 13-17 are pending. Claims 13-15 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 13-17 stand rejected under 35 U.S.C. § 103(a).

Applicants have amended the claims to place the application in condition for allowance. Claim 13 has been amended to include disease states previously presented in currently cancelled claim 16. The amendment is further supported in the specification at page 5, lines 10-16. New claims 18 -28 have been added to further define the Applicants' invention. Support for claims 18 and 19 is found at page 9, line 34 to page 10, line 8 of the specification. New claims 20-28 are supported in the specification at page 5, lines 10-16. These amendments add no new matter.

Rejection of Claims 13-15 under 35 U.S.C. § 112, First Paragraph

Claims 13-15 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement for a method of treating a patient having any disease involving intravascular coagulation. While Applicants do not acquiesce to the merits of the rejection, the claims have been amended to advance prosecution. In particular, the disease states listed in previous claim 16 have been incorporated into presently amended claim 13. As acknowledged by the Examiner, the specification is enabling for a method of treating a patient having one of these disease states.

Applicants respectfully submit that the presently amended claims are enabled and request withdrawal of the rejection of claims 13-15 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 13-17 under 35 U.S.C. § 103(a)

Claims 13-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hirahara, U.S. Patent 5,084,273 (Hirahara) in view of Mochida Pharmaceutical Co. Ltd., JP 08-301786 (Takahashi *et al.*). The Examiner acknowledges that Hirahara in view of Takahashi *et al.* does not provide the claimed weight to weight ratio of about 1 part activated protein C (aPC) to between about 5 to7 parts bulking agent. Rather, the Examiner concludes that the ratio of aPC to bulking agent is a result-effective parameter which was routinely optimized by one of ordinary skill in the art at the time of the invention. Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the court defined the test for determining obviousness under 35 U.S.C. § 103: 1) determine the scope and content of the

prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. The USPTO bears the burden of establishing a *prima facie* case. *(In re Piasecki,* 745 F.2d 1468 (Fed. Cir. 1984)). In order to establish a *prima facie* case, the Examiner must show 1) some suggestion or motivation to modify the reference or to combine reference teachings *(In* re *Fine,* 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention *(Amgen, Inc. v. Chugai Pharmaceutical Co.,* 927 F.2d 1200 (Fed. Cir. 1991)); and 3) the prior art reference or combination of references must teach or suggest all limitations of the claims *(In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991)). Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

Applicants submit that Hirahara is not concerned with use of aPC as the sole active ingredient in a pharmaceutical formulation. Rather, Hirahara is "concerned with anticoagulants containing as the active ingredients human protein C or activated protein C and heparin, or human protein C or activated protein C, heparin and AT III." (emphasis added; column 3, lines 9-12). An essential part of the invention of Hirahara is heparin or heparin and AT III as supported in column 3, lines 28-37, the two examples (column 4, lines, 36-51), and the claims. The examples taught by Hirahara include filling an ampule or vial with protein C or activated protein C, 50 USP units of heparin, 22.5 mg aminoacetic acid, 25 mg of human serum albumin, 100 mg of D-mannitol, and 90 mg of sodium chloride. Nowhere does Hirahara teach or suggest use of aPC in the absence of heparin or heparin coupled with AT III. In fact, Hirahara if anything teaches away from use of aPC as the sole active ingredient, since Hirahara states "Surprisingly, very high anticoagulant activities not obtained with activated protein C alone or with AT III-heparin have been found . . ." (emphasis added; column 3, lines 5-8). Applicants' claims are directed to methods of treatment that utilize formulations of aPC and bulking agents that have enhanced stability through preferred ratios of these ingredients. The present invention does not require heparin or heparin and AT III, and therefore cannot be obvious over Hirahara.

Applicants discovered an important, previously unknown autodegradation pathway of recombinant activated protein C. This discovery led to the development of a method of treatment that utilizes aPC formulations that minimize the formation of des(1-9) and des(1-10) aPC. Thus, the claimed methods of treatment utilize preparations of forms of activated protein C which are more potent than those previously obtained. Since Hirahara does not teach or suggest the formation of des(1-9) and des(1-10) aPC, Hirahara does not provide any

motivation to achieve the present invention by optimizing the aPC to bulking agent ratios toward reducing the formation of these aPC degradation products. Thus, while ratios of aPC used in the formulations taught by Hirahara vary, nowhere does Hirahara teach or suggest the ratios used in the present invention nor does Hirahara provide any motivation to optimize those ratios to minimize aPC degradation products, let alone des(1-9) and des(1-10) aPC. As detailed above, Hirahara also does not teach use of aPC in the absence of heparin or heparin coupled with AT III.

In citing Takahashi et al., the Examiner notes that Takahashi discloses a lyophilized preparation containing a ratio by weight of 1 part aPC to 2.5 parts mannitol. Applicants point out that the compositions taught by Takahashi et al. cannot render the present invention obvious, since the compositions of Takahashi et al. contain a stabilizer, either gelatin or albumin, which is not required by the present invention. In view of the ratio taught by Takahashi et al., the Examiner notes that the ratios in Hirahara may range from 1:67 to 10:1 aPC:bulking agent, and thereby concludes that in the compositions of Hirahara, the ratio can vary widely.

Applicants respectfully submit that Hirahara does not teach such a range of compositions. Rather, Hirahara teaches that the total amount of protein in the active ingredient (which according to Hirahara contains either aPC and heparin or aPC, heparin, and AT III) to be given per dose is in the range of 5 mg to 1 g for an adult weighing 60 kg. In teaching this range per dose, Hirahara does not teach a range of 5 mg to 1 g protein C per preparation. Instead, Hirahara teaches a range of protein C as an active ingredient at a concentration of about 2 μg/ml to 20 μg/ml (column 3, lines 29-31). As an example to further clarify this point, Applicants point out that aPC (Xigris®) is approved in the United States for use in treatment of sepsis at a dosage of 0.024 mg/kg/hr via continuous infusion over a period of up to 96 hours. Xigris® is packaged as a lyophilized product in vials containing 5 or 20 mg aPC. For a 60 kg adult, the total aPC administered in a 96 hour treatment of sepsis would amount to a dose of about 140 mg (0.024 mg/kg/hr X 60 kg X 96 hr = 138.24 mg) (given in a 12 hr maximum infusion per preparation), which could be achieved through use of 28 vials containing 5 mg Xigris®, 7 vials containing 20 mg Xigris®, or various combinations of 5 and 20 mg Xigris® vials.

Combination of Hirahara and Takahashi *et al.* teaches aPC:bulking agent ratios of 1:67 and 1:2.5, with no specific ranges given around these ratios, no indication that overlap may occur between these ratios and/or be beneficial, and in particular, no indication of a ratio of 1:5 to 1:7. Thus, Hirahara in view of Takahashi et al. fails to teach or suggest all of the

limitations of the claimed invention. Moreover, since the aPC degradation products des(1-9) and des(1-10) aPC were previously unknown, Hirahara in view of Takahashi et al. does not provide any motivation to optimize the ratio of aPC to bulking agent. The present invention therefore would not be obvious to one of skill in the art nor obtained through routine optimization of the aPC to bulking agent ratio. Accordingly, the present invention is not obvious over Hirahara in view of Takahashi et al.

In view of the above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments which place the application in condition for allowance. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

Thomas E. LaGrandeur
Attorney for Applicants
Registration No. 51,026
Phone: 317-651-1527

Eli Lilly and Company
Patent Division/TEL
P.O. Box 6288
Indianapolis, Indiana 46206-6288

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